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1. Your reference

ARB/P/118/GBA

2. Patent application number
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0027357.3

9 NOV 2000

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Bradford Particle Design plc
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Bradford BD7 1HR

Patents ADP number *(if you know it)*

7758246002

If the applicant is a corporate body, give the country/state of its incorporation

GB

4. Title of the invention

Particle formation methods and their products

5. Name of your agent *(if you have one)*

Greaves Brewster

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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North Somerset
BS25 1AD

Patents ADP number *(if you know it)*

7885908001

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Country	Piority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number or earlier application	Date of filing *(day / month / year)*

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Yes

a) any applicant named in part 3 is not an inventor, or
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Claim(s)	
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11. I / We request the grant of a patent on the basis of this application.

Signature Carol P Greaves Date 8/11/2000

12. Name and daytime telephone number of person to contact in the United Kingdom: Andrea Brewster 01934 844419

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Particle formation methods and their products

Field of the invention

This invention relates to methods for preparing particles of an active substance which have a layer of an additive, such as a taste masking additive, at the particle surfaces. The invention also relates to the particulate products of such methods.

Background to the invention

There are a number of reasons why a particulate active substance (such as a drug) might need a protective barrier at the particle surfaces. The active substance may be physically or chemically unstable, or incompatible with another substance with which it needs to be formulated. It may need protection against, for example, moisture, light, oxygen or other chemicals. A surface coating may alternatively be needed to delay release of the active substance for a desired time period and/or until it reaches an appropriate site, or to target its delivery to such a site. Drugs intended for oral administration may need coatings to mask their flavour and render them more palatable to patients.

To protect an active substance in this way, one or more protective additives need to be coated onto the external surfaces of the active particles. Several methods are known for applying such coatings. Traditional pan or fluidised bed techniques apply a fluid coating directly to solid active particles. Alternatively, a thin film layer of a coating material may be deposited onto particle surfaces by adding the particles to a solution of the coating material and then removing the solvent, for instance by evaporation, spray drying or freeze drying. Plasticisers, such as polyethylene glycol (PEG) may be added to the solution to enhance coating flexibility and surface adhesion. This technique is widely used in the pharmaceutical industry to coat solid drug dosage forms such as tablets, granules and powders.

With changing trends in drug delivery, there is a growing need for direct coating of drug particles, especially fine particles. Traditional coating methods, as described above, involve several stages such as crystallising, harvesting, drying, milling and sieving of the drug to obtain particles of the desired size range, and a subsequent, separate, coating step. This increases the risks of product loss and contamination.

The coating of microfine particles, for instance in the range 0.5-100 μm, has often proved particularly problematic due to the large surface area of the particles and the non-uniform, often incomplete, coatings achieved using traditional pan or fluidised bed coating techniques. If the material to be coated is water soluble, organic solvents are needed for the coating solution, which can lead to toxicity, flammability and/or environmental problems.

In the particular case of taste masking coatings, the need for a continuous and uniform coating layer is particularly great, since any discontinuity in the coating, allowing release of even the smallest amount of a poor tasting active substance, is readily detectable. Thus, the above described problems with prior art coating techniques assume even greater significance in the case of taste masking.

Recent developments in the formation of particulate active substances include processes using supercritical or near-critical fluids as anti-solvents to precipitate the active substance from solution or suspension. One such technique is that known as SEDS™ ("Solution Enhanced Dispersion by Supercritical fluids"), which is described in WO-95/01221 and, in various modified forms, in WO-96/00610, WO-98/36825, WO-99/44733, WO-99/59710 and/or our co-pending PCT patent applications nos. PCT/GB00/02606 and PCT/GB00/03328. The literature on SEDS™ refers to the possibility of coating fine particles, starting with a suspension of the particles in a solution of the coating material (see in particular WO-96/00610, page 20 line 28 – page 21 line 2, also WO-95/01221 Example 5). However, again the particles must be prepared beforehand and coated in a separate step.

Distinct from the coating of particulate actives, it is also known to mix active substances such as drugs with excipients (typically polymers) which serve as carriers, fillers and/or solubility modifiers. For this purpose the active substance and excipient are ideally *co*formulated to yield an intimate and homogeneous mixture of the two. Known techniques include co-precipitation of both the active and the excipient from a solvent system containing both. The SEDS™ process may also be used to coformulate in this way, as described for instance in WO-95/01221 (Examples 10 and16) and/or our co-pending PCT patent applications nos. PCT/GB00/02606 (Examples 1-4) and PCT/GB00/03328.

The products of coformulation processes are generally intimate mixtures of the species precipitated, for instance a solid dispersion of a drug within a polymer matrix. This is particularly the case for the products of a very rapid particle formation process such as SEDS™ (see the above literature). Indeed, because prior art coformulations have for the most part been motivated by the need to modify the dissolution rate of an active substance, they have concentrated (as in our co-pending PCT patent application no. PCT/GB00/03328) on obtaining truly intimate, homogeneous mixtures of the active and excipient(s), with the active preferably in its more soluble amorphous, as opposed to crystalline, state.

Whilst such a high degree of mixing is desirable for many products, it is clearly not appropriate where the additive is a surface protector or taste masking agent, since it leaves at least some of the active substance exposed at the particle surfaces, whilst "tying up" a significant proportion of the additive within the particle core. In the case of an unpleasant-tasting drug, even very tiny amounts at the particle surfaces can be sufficient to stimulate the taste buds, despite the additional presence of a taste masking agent.

Thus, coformulation, in particular via SEDS™, has not previously been used to coat active substances with protective agents such as taste maskers.

Statements of the invention

It has now surprisingly been found, however, that the SEDS™ process can be used, in some cases, to prepare a particulate coformulation of an active substance and an additive, generally a protective additive, in which the active substance *is* sufficiently protected, at the particle surfaces, for the process to be of use in preparing taste masked or otherwise surface-protected drugs. The process can generate particles in which the active substance:additive concentration ratio varies with diameter, the surface having a sufficiently high additive concentration to "protect" (which includes masking) the active substance, but the core of the particle containing a significantly higher concentration of the active substance. Thus, although the particles are not strictly "coated", ie, they generally possess no distinct physical boundary between a core and a coating layer, nevertheless they can behave as though coated.

In this way, SEDS™ can provide an extremely advantageous method for "coating" and protecting active substances. The SEDS™ process, as discussed in WO-95/01221 and the other documents listed above, can bring with it a number of general advantages, such as environmental friendliness, versatility and an extremely high degree of control over the physicochemical properties (particle size and morphology, for example) of the product. It also allows the single-step production of multi-component products.

According to a first aspect of the present invention there is therefore provided a method for preparing particles of an active substance having a (typically protective) layer of an additive at the particle surfaces, the method involving dissolving both the active substance and the additive in a vehicle to form a target solution, and contacting the target solution with an anti-solvent fluid using a SEDS™ particle formation process, to cause the active substance and additive to coprecipitate.

In the following description, references to the crystallinity, morphology, particle growth rate, solubility and miscibility of a material refer to the relevant properties under the operating conditions (for example, pressure, temperature, nature of reagents) used.

By "active substance" is meant a substance capable of performing some useful function in an end product, whether pharmaceutical, nutritional, herbicidal, pesticidal or whatever. The term is intended to embrace substances whose function is as a carrier, diluent or bulking agent for the additive (for instance, in food products, a polymer such as a cellulosic polymer may be coated with a pleasant tasting additive such as a sugar, to yield a product having the desired flavour but with a reduced additive concentration).

The active substance may be a single active substance or a mixture of two or more. It may be monomeric, oligomeric or polymeric, organic (including organometallic) or inorganic, hydrophilic or hydrophobic. It may be a small molecule, for instance a synthetic drug like paracetamol, or a larger molecule such as a (poly)peptide, an enzyme, an antigen or other biological material. It preferably comprises a pharmaceutically active substance, although many other active substances, whatever their intended function (for instance, herbicides, pesticides, foodstuffs, nutriceuticals, dyes, perfumes, cosmetics, detergents, etc..), may be coformulated with additives in accordance with the invention.

In particular the active substance may be a material (such as a drug) intended for consumption, which has an unpleasant taste and/or odour and needs to be coated with a taste masking agent. Examples include the bitter tasting anti-malarial drugs quinine sulphate and chloroquine; many oral corticosteroids such as are used for asthma treatment; dicyclomine HCl (anti-spasmodic); dipyridamole (platelet inhibitor); Toprimate (anti-epileptic); Oxycodone (analgesic); Carispodol (used in the treatment of hyperactivity of skeletal muscles); Bupropion (anti-depressant); Sumatripan (used in migraine treatment); Verapamil HCl (calcium ion flux inhibitor); Tinidazole (anti-parasitic); acetyl salicylic acid (Aspirin, anti-pyretic); Cimetidine HCl (used in the treatment of acid/peptic disorders); Diltiazem HCl (anti-anginal) and Orphenadrine citrate (anti-muscarinic). Clearly this list is not exhaustive.

Alternatively the active substance may be a material which requires a protective coating because it is sensitive to light, moisture, oxygen, chemical contaminants or other environmental influences, or because of its incompatibility with other materials with which it has to be stored or processed.

Active substance instability can be a particularly acute problem in the case of pharmaceuticals, since degradation can lead not only to a reduction in the active substance concentration or its bioavailability, but also in cases to the generation of toxic products and/or to an undesirable change in physical form or appearance. The most common reasons for degradation of drug substances exposed to atmospheric stresses are oxidation, hydrolysis and photochemical decomposition.

Drugs susceptible to hydrolysis typically contain one or more of the following functional groups: amides (eg, as in dibucaine, benzyl penicillin, sodium chloramphenicol and ergometrine); esters (eg, as in procaine, tetracaine, methyladopate and physostigmine); lactams (eg, as in cephalosporin, nitrazepam and chlorodiazeproxide); lactones (eg, as in pilocarpine and spironolactone); oximes (eg, as in steroid oximes); imides (eg, as in glutethimide and ethosuximide); malonic urease (eg, as in barbiturates); and nitrogen mustards (eg, as in melphalan).

Drugs that undergo photochemical decomposition include hydrocortisone, prednisolone, ascorbic acid (vitamin C), phenothiazine and folic acid. Those that can be affected by oxidative degradation, often under ambient conditions, include morphine, dopamine, adrenaline, steroids, antibiotics and vitamins.

The additive may also be a single substance or a mixture of two or more, and may be monomeric, oligomeric or polymeric (typically either oligomeric or polymeric). It may be organic (including organometallic) or inorganic, hydrophilic or hydrophobic. It is typically a substance capable of protecting an active substance from external effects such as heat, light, moisture, oxygen or chemical contaminants, and/or of reducing incompatibilities between the active substance and another material with which it needs to be processed or stored, and/or of delaying, slowing or targetting the release of the active substance (for instance, for drug delivery systems), and/or of masking the flavour and/or odour of an active substance, when applied to the surface of the active substance.

The additive may in particular be a taste and/or odour masking agent, in which case it should be a flavour and odour-free, or at least a pleasant tasting and smelling material,

preferably hydrophobic, which is not significantly degraded by saliva during the typical residence times of a consumable product, such as a drug or foodstuff, in a patient's mouth.

Instead or in addition, the function of the additive may be to delay release of the active substance and/or to target its delivery to a predetermined site. This is of particular use when the active substance is a pharmaceutical (for example, drug delivery can be targetted to the intestines and colon using a coating which is insoluble in gastric fluids), but may be necessary for instance to delay the onset of any chemical reaction involving the active substance.

In some cases, the additive may itself be an "active" substance such as a drug, for instance where two or more drugs are to be co-administered but one must be released before another.

Examples of pharmaceutically acceptable additives include celluloses and cellulose derivatives (eg, ethyl cellulose (hydrophobic coating agent), hydroxyethyl cellulose (commonly used for tablet coatings), hydroxypropyl cellulose and hydroxypropyl methyl cellulose); hydroxypropyl methyl phthalate (used as an enteric coating for tablets and granules); polymethyl acrylates (Eudragit™); vinyl polymers such as polyvinyl alcohol; and homo- and co-polymers of hydroxy acids such as lactic and glycolic acids. These are all amorphous or, in the case of (co)polymers incorporating lactic acid, semi-crystalline. Other commonly used coating materials include shellac, carnauba wax and microcrystalline wax. The additive may be or contain flavourings, including sugars and sweeteners. Again, these lists are by no means exhaustive.

Preferred additives are those which are amorphous or semi-crystalline, most preferably amorphous, in nature.

The active substance and/or the additive may be formed from an *in situ* reaction (ie, a reaction carried out immediately prior to, or on, contact with the anti-solvent fluid) between two or more reactant substances each carried by an appropriate vehicle.

The vehicle is a fluid capable of dissolving both the active substance and the additive, the solubility of the active substance and the additive in the vehicle being preferably 10^{-4} mole % or greater. It must be miscible in the anti-solvent fluid under the operating conditions used to carry out the SEDS™ process. (By "miscible" is meant that the two fluids are miscible in all proportions, and/or that they can mix sufficiently well, under the operating conditions used, as to achieve the same or a similar effect, ie, dissolution of the fluids in one another and precipitation of the active substance and additive.)

The term "vehicle" includes a single fluid or a mixture of two or more fluids, which are typically liquids but may be, for instance, supercritical or near-critical fluids. In the case of a vehicle comprising two or more fluids, the overall mixture should have the necessary solubility and miscibility characteristics vis-à-vis the active substance, the additive and the anti-solvent fluid.

The vehicle or its component fluids may contain, in solution or suspension, other materials apart from the active substance and additive.

The selection of an appropriate vehicle depends on the active substance, the additive and the anti-solvent fluid as well as on the chosen operating conditions (including pressure, temperature and fluid flow rates). Based on the above guidelines as to the miscibility and solubility characteristics of the fluids involved, the skilled person would be well able to select suitable materials with which to carry out the method of the invention.

When the vehicle is composed of two or more fluids, for instance an organic solvent with a minor amount of a co-solvent "modifier", or a water/organic solvent mixture, the two or more fluids may be mixed, so as to form the target solution, *in situ*, ie, at or immediately before the target solution contacts the anti-solvent fluid and particle formation occurs. Ideally this occurs at the outlet of a nozzle used to co-introduce the fluids into a particle formation vessel. For example, a first fluid in which the active substance is dissolved may be introduced through one passage of a multi-passage coaxial nozzle as described in WO-96/00610 (Figures 3 and 4) or our co-pending PCT patent application number PCT/GB00/02606 (Figure 4). A second fluid, in which the additive

is dissolved, may be introduced through another passage of the nozzle. The nozzle passage outlets may be arranged to terminate adjacent one another at the entrance to the particle formation vessel, in a way that allows the two fluids to meet and mix inside the nozzle, immediately before coming into contact with an anti-solvent fluid introduced through another nozzle passage. Both fluids will be extracted together into the anti-solvent fluid, resulting in coprecipitation of the active substance and the additive. For this to work, at least one of the vehicle fluids should be miscible, or substantially so, in the anti-solvent fluid. Ideally, although not necessarily (as described in our co-pending PCT patent application no. PCT/GB00/02606), the two vehicle fluids should be miscible or substantially miscible with one another.

Such *in situ* mixing of vehicles may be particularly useful if there is no readily available common solvent for the active substance and the additive (for instance, when one material is organic and the other inorganic), or if the active substance and additive solutions are in some way incompatible.

The anti-solvent fluid is a fluid, or a mixture of fluids, in which both the active substance and the additive are for all practical purposes (in particular, under the chosen operating conditions and taking into account any fluid modifiers present) insoluble or substantially insoluble. By "insoluble" is meant that the anti-solvent cannot, at the point where it extracts the vehicle, extract or dissolve the active substance or additive as particles are formed. Preferably the active substance and the additive are less than 10^{-5} mole %, more preferably less than 10^{-7} mole %, soluble in the anti-solvent fluid.

The anti-solvent fluid is preferably a supercritical or near-critical fluid under the operating conditions used. By "supercritical fluid" is meant a fluid at or above its critical pressure (P_c) and critical temperature (T_c) simultaneously. In practice, the pressure of the fluid is likely to be in the range $(1.01 - 9.0)P_c$, preferably $(1.01 - 7.0)P_c$, and its temperature in the range $(1.01 - 4.0)T_c$ (where T_c is measured in Kelvin). However, some fluids (eg, helium and neon) have particularly low critical pressures and temperatures, and may need to be used under operating conditions well in excess of (such as up to 200 times) those critical values.

The term "near-critical fluid" encompasses both high pressure liquids, which are fluids at or above their critical pressure but below (although preferably close to) their critical temperature, and dense vapours, which are fluids at or above their critical temperature but below (although preferably close to) their critical pressure.

By way of example, a high pressure liquid might have a pressure between about 1.01 and 9 times its P_c, and a temperature between about 0.5 and 0.99 times its T_c. A dense vapour might, correspondingly, have a pressure between about 0.5 and 0.99 times its P_c, and a temperature between about 1.01 and 4 times its T_c.

The anti-solvent is preferably a supercritical fluid such as supercritical carbon dioxide, nitrogen, nitrous oxide, sulphur hexafluoride, xenon, ethane, ethylene, chlorotrifluoromethane, chlorodifluoromethane, dichloromethane, trifluoromethane or a noble gas such as helium or neon, or a supercritical mixture of any of these. Most preferably it is supercritical carbon dioxide.

The vehicle and/or the anti-solvent fluid may contain one or more modifiers, for example water, methanol, ethanol, isopropanol or acetone. A modifier (or co-solvent) may be described as a chemical which, when added to a fluid such as a supercritical or near-critical fluid, changes the intrinsic properties of that fluid in or around its critical point, in particular its ability to dissolve other materials. When used, a modifier preferably constitutes not more than 40 mole %, more preferably not more than 20 mole %, and most preferably between 1 and 10 mole %, of the vehicle or anti-solvent fluid.

The anti-solvent flow rate will generally be chosen to ensure an excess of the anti-solvent over the target solution when the fluids come into contact, to minimise the risk of the vehicle re-dissolving and/or agglomerating the particles formed. At the point of extraction the vehicle may typically constitute 80 mole % or less, preferably 50 mole % or less or 30 mole % or less, more preferably 20 mole % or less and most preferably 5 mole % or less, of the fluid mixture formed.

By "a SEDS™ process" is meant a particle formation process as described in WO-95/01221, WO-96/00610, WO-98/36825, WO-99/44733, WO-99/59710 and/or our co-pending PCT patent applications nos. PCT/GB00/02606 and/or PCT/GB00/03328, in which a supercritical or near-critical fluid anti-solvent is used simultaneously both to disperse, and to extract a fluid vehicle from, a solution or suspension of a target substance. Such a technique can provide better, and more consistent, control over the physicochemical properties of the product (particle size and size distribution, particle morphology, etc..) than has proved possible for coformulations in the past.

Because the present invention is a modified version of that disclosed in the above listed patent applications, technical features of the processes described in those documents can apply also to the present invention. The earlier documents are therefore intended to be read together with the present application.

The concentration of the active substance and the additive in the target solution must be chosen to give a desired active:additive ratio in the final product. Particularly preferred are relatively high levels of the additive, for instance 10%, 20% or 30% w/w or greater, more preferably 40% w/w or greater, most preferably 50% or 60% or 70% or 75% or 80% w/w or greater.

The coprecipitated product of the process of the invention is a solid dispersion, each particle containing an intimate molecular-level mixture of both the active substance and the additive. However, it has surprisingly been found that in certain cases the product is not a homogeneous mixture of the two components, but has a significantly lower level of the active substance at and near the surface of each particle compared to that in the particle core, sufficient for the additive to form, in effect, a protective surface layer. Thus, for example, a taste masking additive can mask even a strongly flavoured active substance, whilst at the same time also being incorporated into the sub-surface core of each particle. There is typically, however, no distinct physical boundary between the protective surface "layer" and the "enclosed" core, but instead a gradual change, with a finite gradient, in the active:additive ratio. The particle constitution is that of a solid dispersion throughout, but with varying additive concentration across its radius.

It has also, surprisingly, been found that for certain active/additive systems, in particular certain drug/polymer systems, SEDS™ coformulation does not readily yield an amorphous phase active, even up to in some cases 80% w/w additive. Instead the coformulated product contains crystalline active substance with a relatively high additive concentration at the particle surfaces.

The process of the invention works particularly well, it is believed (although we do not wish to be bound by this theory), when the active substance precipitates more quickly than the additive under the operating conditions (including choice of solid and fluid reagents) used. More specifically, this occurs when the nucleation and/or particle growth rate of the active substance is higher than that of the additive. The quicker growing active substance appears to precipitate initially as a "core" particle, around which both the active and the additive collect as the solid particles grow, with the relative concentration of the slower growing additive gradually increasing as the particles grow in diameter. Towards the outer surfaces of the particles, when most of the active present has already precipitated, the concentration of the additive becomes sufficiently high that it then effectively "coats" the active-rich core.

Thus, the operating conditions and/or the reagents used in the method of the invention should ideally be chosen so as to enhance or maximise the difference between the precipitation rates of the active substance and the additive. (By "precipitation rate" is meant the combined effects of the nucleation and particle growth rates.) This may in turn mean enhancing or maximising the chance of phase separation occurring, between on the one hand the active substance and its associated vehicle and on the other hand the additive and its associated vehicle, immediately prior to or at the point of particle formation; phase separation can inhibit formation of a truly homogeneous solid dispersion between the active and additive.

Certain active/additive pairs will already have significantly different precipitation rates. This appears particularly to be the case when the active substance precipitates in a crystalline form and the additive in an amorphous form. Differences in crystal habit may also affect the active substance precipitation rate. For example, it has been found that the

invented process can be effective for active substances having a needle-like crystalline habit, possibly because the crystal growth rate is significantly faster in one dimension than in the others. Generally speaking, the active substance may have a crystalline form (under the conditions used) which is significantly longer in one dimension than in at least one other dimension, and/or its crystals may grow significantly faster in one dimension than in at least one other dimension; this embraces for example needle-like crystals and also, potentially, wafer- or plate-like crystals (for which growth is faster in two dimensions than in the third) and elongate prism-shaped crystals. Active substances having other crystal habits may of course be protected using the method of the invention, using operating conditions suitable to enhance the difference between the active and additive precipitation rates.

In the above discussion, "significantly" longer or faster means approximately 5% or more, preferably at least 10% or 20% or 30%, greater than the length or speed of the lower of the two parameters being compared.

The present invention may also be effective when the active substance and the additive have significantly different (for instance, at least 5% different, preferably at least 10%, more preferably at least 20% or 30%, based on the lower of the two values) solubilities in the anti-solvent fluid, as this can also affect the relative precipitation rates of the active and additive particles. This effect could be enhanced by the inclusion of suitable modifiers in the anti-solvent fluid, and/or by introducing a "secondary" anti-solvent fluid, having a lower capacity than the main anti-solvent for extracting the vehicle, as described in WO-99/44733. Generally, the additive should be more soluble than the active substance in the anti-solvent fluid, which should promote precipitation of the additive nearer to the particle surfaces.

Similarly, when the active substance and additive have low solubilities (for instance, less than 30% w/w, preferably less than 25% w/w, more preferably less than 20% or 15% or 10% w/w) in one another, ie, a low affinity for one another or a low miscibility with one another, this too can affect their relative precipitation rates. Thus, the active substance and additive might preferably have significantly different (for instance, at least 5%

different, preferably at least 10% or 20%, based on the lower of the two values) polarities and thus low mutual solubilities and a low mutual affinity – this is likely to reduce interaction between the active and additive during particle formation, and promote the growth of active-rich and additive-rich regions in the product particles.

Instead or in addition, the operating conditions may be modified to enhance the difference between the active and additive precipitation rates. Operating under relatively mild temperatures and/or pressures (for instance, only just above the critical temperature and/or pressure of the supercritical solution formed between the anti-solvent fluid and the vehicle) may be expected to enhance any inherent differences in particle precipitation rates, by reducing the vehicle extraction rate and maximising the chance of phase separation between the active and additive components.

Typically, such "mild" conditions might correspond to between 1 and 1.1 times the critical temperature T_c (in Kelvin) of the anti-solvent fluid, preferably between 1.01 and 1.1 times T_c, more preferably between 1.01 and 1.03 times T_c. The pressure may be between 1 and 1.5 times the critical pressure P_c, preferably between 1.05 and 1.4 times P_c, more preferably between 1.08 or 1.1 and 1.35 times P_c. In the particular case of a carbon dioxide anti-solvent (T_c = 304 K; P_c = 74 bar), typical operating temperatures might be between 304 and 313 K, and operating pressures between 80 and 100 or 120 bar.

As described above, the method of the invention may be practised using two separate vehicle fluids, one carrying the active substance and one carrying the additive, which contact one another only at or immediately before their point of contact with the anti-solvent fluid (ie, the point of vehicle extraction and particle formation). If the two vehicle fluids have significantly different solubilities in the anti-solvent fluid, this can cause a small degree of phase separation at the point of particle formation, the extent of which depends, inter alia, on the time period between the vehicles mixing and their contact with the anti-solvent fluid (which in turn depends on the fluid flow rates and the internal geometry of the fluid inlet used), and again can lead to differences in precipitation rate between the active and the additive. Generally speaking, any difference

in the rate of vehicle extraction, by the anti-solvent fluid, between the active substance containing solution and that carrying the additive, is thought to be able to increase the effectiveness of the present invention. Rate of solvent extraction is in turn influenced by the molecular interactions between each solute and its respective solvent, high levels of interaction being likely to slow solvent extraction and delay or discourage precipitation. Modifiers (co-solvents) in one or more of the vehicle fluid(s) and/or the anti-solvent fluid may be chosen to enhance such effects; operating pressures and temperatures, and even fluid flow rates, may also influence them.

A semi-crystalline or in particular an amorphous additive will also typically have a relatively high viscosity on dissolution in an appropriate vehicle. This viscosity increase can impede solvent removal during precipitation and subsequent drying, again slowing the particle formation process and allowing an active substance to precipitate more rapidly to form the core of a coformulated product in accordance with the invention.

The method of the invention preferably involves selecting the reagents (ie, the active substance, the additive, the vehicle, the anti-solvent fluid and any modifiers or co-solvents present) and the operating conditions (such as temperature and pressure at the point of particle formation, fluid flow rates and concentrations of the active and the additive in the vehicle), in order to increase the difference in particle precipitation rates, under the conditions used, between the active substance and the additive. Preferably the precipitation rate difference is at least 5% of that of the slower precipitating material, more preferably at least 10%, most preferably at least 20% or 30% or 40% or 50% or 75% or 90% or 100%.

It can be seen from the above that there are several potential ways in which the precipitation rate difference may be enhanced or maximised in accordance with the invention.

The method of the invention provides significant advantages over known methods for coating an active substance with an additive. Because it involves particle formation by SEDS™ it is a one-step process, which can be carried out in a closed environment,

shielded if necessary from light, oxygen and other contaminants, and it allows excellent control over the physicochemical characteristics of the product (such as particle size and size distribution, morphology, purity and yield), as described in the prior art on SEDS™. It is also extremely useful for formulating small particles, which can otherwise be difficult to coat.

The coformulated particles made according to the invention differ from conventional coated products; they are solid dispersions of one material in another, but with a finite gradient in the relative concentration of the additive, which concentration increases radially outwards from the core to the surface of each particle. The particles are thus not truly homogeneous mixtures of the two components, such as one would expect from a prior art coformulation process, since such mixtures would include at least some exposed active substance at the particle surfaces and hence be unsuitable for protecting or masking the active substance. In particles made according to the present invention, the active substance:additive ratio, at the particle surface, can be sufficiently low for a taste masking additive to mask, effectively, the flavour of for example an extremely bitter tasting drug such as quinine sulphate.

Nor, however, are the particles "coated", in the conventional sense of the word, with the additive. They tend not to possess a core and a separate coating layer with a distinct physical boundary (at which boundary the "gradient" in the additive concentration is theoretically infinite) between them. Rather, they exhibit a gradual change from an active-rich core to an additive-rich (and preferably active-free) surface.

These properties of the particles, thought to be unique, are likely to influence their dissolution profiles, in particular where the additive acts to inhibit release of the active substance. The release-inhibiting effect is likely to be most marked during an initial period of time corresponding to dissolution of the additive at the particle surfaces, and to fall off gradually thereafter.

Differential scanning calorimetry (DSC) data from the products is also likely to be affected by their unique active:additive concentration profile. For instance, when the

additive is crystalline or semi-crystalline, it is expected that a DSC profile for a product according to the invention will exhibit two distinct peaks, one for the active substance and one for the additive, with both peaks broader at least to some degree than those for the pure starting materials, indicating a degree of solid/solid interaction but retention of at least some regions of the individual materials.

Similarly, X-ray diffraction (XRD) analysis of a product according to the invention is likely to indicate reduced crystallinity for a normally crystalline active substance, due to interaction with the additive.

The gradient in the relative additive concentration, across the particle radius, will depend on a number of factors such as the solubility characteristics of the species present, the viscosities of their solutions, the nature and rate of their particle growth, etc.., as described above. The gradient may or may not be constant across the radius, but the rate of change in additive concentration is typically continuous rather than stepped, from the core to the additive-rich surface (which preferably contains, at its outer limit, 100% additive). It may be possible to identify "core" and "surface" regions of the particles with a concentration gradient between them. In this case the "core" preferably contains between 90 and 100% of the active substance, more preferably between 95 and 100%, most preferably between 98 and 100% w/w (it is unlikely, although theoretically possible, that the core will contain no additive at all). The active substance in the core is preferably in a crystalline form, for instance between 80% and 100% or between 90 and 100%, ideally 100% crystalline. The "surface" layer preferably contains between 5 and 0%, more preferably between 2 and 0% or between 1 and 0% or between 0.5 and 0%, most preferably 0% w/w of the active substance.

The concentration gradient can be controlled, in the method of the invention, by altering the operating conditions as described above. It will be affected by these and by the nature of in particular the active substance and the additive but also the vehicle and the anti-solvent fluid. The skilled person, using available data on the solubilities, miscibilities and viscosities of the reagents he uses, should be well able to select and alter

the operating conditions to influence the distribution of the additive in the product particles.

According to a second aspect of the present invention, there is provided a particulate coformulation of an active substance and a (typically protective) additive, which coformulation is a solid dispersion of one component in the other but with a finite gradient in the relative additive concentration which increases radially outwards from the core to the surface of the particles, the particles having an additive-rich surface region but preferably no distinct physical boundary between that region and the rest of the particle. The additive concentration gradient is preferably as described above.

Alternatively, a particulate coformulation in accordance with the invention may be described as an intimate, molecular level, solid-phase mixture of an active substance and an additive, the particles of which have an additive-rich, preferably active substance-free, surface region.

In the case where the active substance has an unpleasant flavour or odour and the additive is a taste masking agent, the active substance:additive weight ratio, at the particle surfaces, is preferably sufficiently low for the additive to mask, effectively, the flavour or odour of the active substance.

A coformulation according to the second aspect of the invention is preferably made by a method according to the first aspect. Aspects of the coformulation such as the nature of the active substance and the additive are therefore preferably as described above in connection with the first aspect of the invention. The coformulation may in particular be or comprise a pharmaceutical or nutriceutical agent or a foodstuff.

A third aspect of the invention provides a pharmaceutical composition which includes a coformulation according to the second aspect. A fourth aspect provides a foodstuff or nutriceutical composition which includes a coformulation according to the second aspect.

A fifth aspect provides the use of a SEDS™ process in preparing particles of an active substance having a layer of an additive on the particle surfaces, the method involving dissolving both the active substance and the additive in a vehicle to form a target solution, and contacting the target solution with an anti-solvent fluid using a SEDS™ particle formation process, to cause the active substance and additive to coprecipitate.

The present invention will now be described, by way of example only, with reference to the accompanying illustrative drawings, of which:

Figures 1 to 11 are scanning electron microscope (SEM) photographs of some of the products and starting materials for Examples A1 to A10 below;

Figures 12 to 14 are X-ray diffraction (XRD) patterns for pure quinine sulphate and the products of Examples A6 and A8 respectively;

Figures 15 to 23 are SEM photographs of some of the products and starting materials for Examples B1 to B3, C1 and C2 below; and

Figures 24 and 25 are XRD patterns for pure sodium chloride and the product of Example C1 respectively.

Experimental Examples A

These examples demonstrate the coformulation, using SEDS™, of the anti-malarial drug quinine sulphate (QS) (Sigma, UK) with ethyl cellulose (EC-N7, Hercules, UK). QS has an unpleasant bitter taste and would conventionally need to be coated with a taste masking agent prior to administration. A SEDS™ process was used to precipitate both drug and polymer together from a single "target solution". The apparatus used was analogous to that described in WO-95/01221 (Figure 1), using a 50 ml Keystone™ pressure vessel as the particle formation vessel and a two-passage concentric nozzle of the form depicted in Figure 3 of WO-95/01221. The nozzle outlet had an internal

morphology with smooth surfaces – see the representative SEM photographs in Figures 4, 5 and 6 for the products of Examples A3; A4 and A6 respectively.

The Example A8 product (60% w/w ethyl cellulose) contained spherical particles, most likely of ethyl cellulose, deposited on the edges of needle-like particles (see Figures 7 and 8). This effect became more marked as the ethyl cellulose content increased, the spherical polymer particles covering almost all the QS crystal surfaces in the products of Example 9A (70% w/w ethyl cellulose, Figure 9) and 10A (80% w/w ethyl cellulose, Figures 10 and 11).

Results and discussion

The X-ray diffraction (XRD) patterns for the products of Examples A2 to A10 were essentially similar (in terms of peak positions) to that of the pure, unprocessed QS powder (Figure 12). This indicates that there had been no solid state phase (polymorphic) change in the QS during SEDS™ processing and that its crystalline phase was still present in all products. In other words, the products were not true solid "dispersions" of the drug in the polymer (as were, for example, the products described in our co-pending PCT patent application number PCT/GB00/03328) but still contained at least two distinct solid phases. Figures 13 and 14 show the XRD patterns for the products of Examples A6 and A8 respectively; a slight reduction in crystallinity can be observed, which is consistent with the presence of the polymer in the surface regions of the particles.

The XRD data are also consistent with the SEM observations of crystalline particles with polymer-like features on the particle surfaces.

When coformulating a drug with more than about 40% w/w of a polymer, in general an amorphous particulate product would be expected. Typically, even at levels below 40% w/w, the presence of the polymer would still be expected to cause a substantial decrease in the degree of drug crystallinity. This is illustrated and confirmed by the teachings in our co-pending PCT patent application number PCT/GB00/03328. It is therefore

preparations) products. It was chosen for these experiments because of the ease with which it can be detected if insufficiently taste masked.

The aspartame and ethyl cellulose were precipitated together from a single "target solution" in a 1:1 v:v acetone:methanol solvent mixture. The apparatus and operating conditions (temperature, pressure and fluid flow rates) used were the same as those in Examples A. Again the anti-solvent was supercritical carbon dioxide.

Example B1 – coprecipitation of aspartame and ethyl cellulose

The target solution contained 1% w/v aspartame and 10% w/w ethyl cellulose. The product collected in the particle formation vessel was a fine, fluffy white powder. SEM examination showed a needle-like morphology (Figures 16 and 17), similar to that of the aspartame starting material (Figure 15), but with small spherical polymer particles visible on the aspartame crystal surfaces even at this relatively low polymer concentration (Figure 17).

Examples B2 and B3 – increasing the polymer concentration

Example B1 was repeated but with ethyl cellulose concentrations of 30 and 60% w/w respectively in the target solution. In both cases the product was a fine, fluffy white powder with similar morphology to that of Example B1, although at these levels the polymer particles appeared completely to cover the aspartame crystals. Figure 18 is an SEM photograph of the Example B2 product (30% w/w ethyl cellulose); Figures 19 and 20 show that of Example B3 (60% w/w ethyl cellulose).

The Example B2 product (30% w/w ethyl cellulose) was tasted by seven panellists. No sweetness was detected for more than 600 seconds. In contrast, sweetness could be detected immediately from the as-supplied aspartame starting material. The taste masking effect is believed to be due to the hydrophobic ethyl cellulose layer covering virtually every aspartame particle (Figure 18).

Experimental Examples C

In these experiments, the method of the invention was used to apply a taste masking coating to an active substance (NaCl) precipitated from an aqueous solution. Two alternative processing methods were used (Experiments C1 and C2). The products of both experiments were tasted by five panellists. Very little if any saltiness was detected for more than 300 seconds, indicating efficient coating of the NaCl with the taste masking additive.

These results illustrate further the broad applicability of the present invention.

Example C1 – in situ mixing of active and additive solutions

A three-passage coaxial nozzle, of the type illustrated in Figure 3 of WO-96/00610, was used to co-introduce into a 50 ml Keystone™ pressure vessel (a) a 30% w/v solution of pure NaCl (>99%, Sigma UK) in deionised water, (b) a 0.22% w/v solution of EC-N7 (as in Examples B) in pure methanol and (c) supercritical carbon dioxide as the anti-solvent. The NaCl and EC-N7 solutions, introduced through the intermediate and inner nozzle passages respectively, met inside the nozzle immediately prior to their contact with carbon dioxide flowing through the outer nozzle passage.

The flow rates for the fluids were (a) 0.02 ml/min, (b) 1.2 ml/min and (c) 36 ml/min. The pressure vessel was maintained at 100 bar and 35°C. The nozzle outlet had an internal diameter of 0.2 mm.

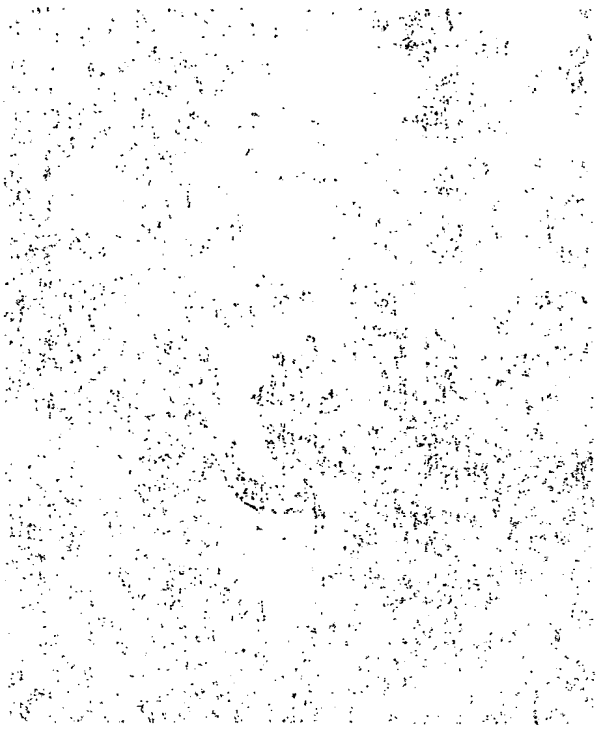
The relative NaCl and EC-N7 concentrations yielded a coformulation containing 30% w/w of the ethyl cellulose. The product was a fine, fluffy, white powder; SEM analysis showed microparticles with a rounded morphology (Figure 22) which were much smaller than those of the as received, milled pure NaCl (Figure 21).

Figures 24 and 25 are XRD patterns for the NaCl starting material and the Example C1 product respectively. That for the C1 product indicates a slight reduction in crystallinity compared to that for the starting material, due to the presence of the polymer.

Example C2 – pre-mixing of active and additive solutions

In this experiment, 0.3 g of pure NaCl was dissolved in 1 ml of deionised water to form solution A. 0.13 g of EC-N7 was dissolved in 60 ml of pure methanol to form solution B. Solution B was then added to solution A to form a solution mixture C. Mixture C was then pumped at 0.3 ml/min into a 50 ml Keystone™ vessel kept at 100 bar and 35°C, via the inner passage of a two-passage coaxial nozzle (outlet diameter 0.2 mm) as used in Examples B. Supercritical carbon dioxide was introduced at 9 ml/min through the outer nozzle passage.

The product was a fine, fluffy white powder (SEM photomicrograph shown in Figure 23) having a similar morphology to that of the Example C1 product.



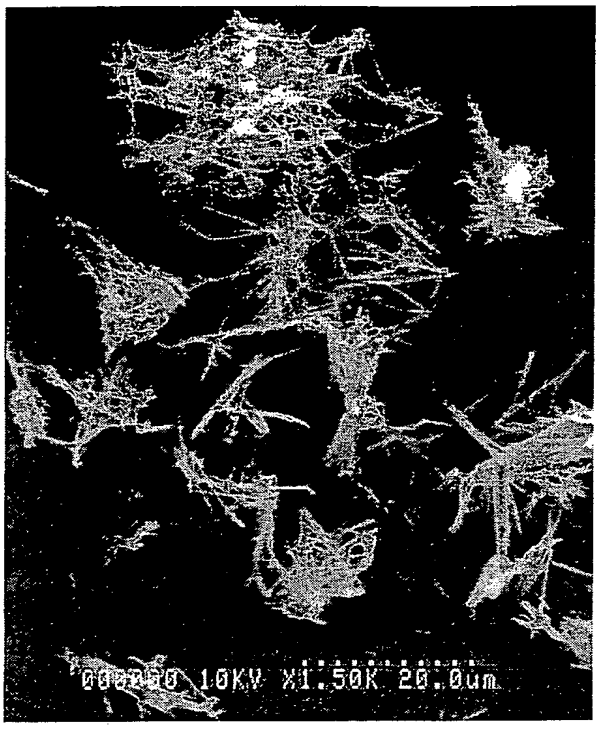


Figure 1.

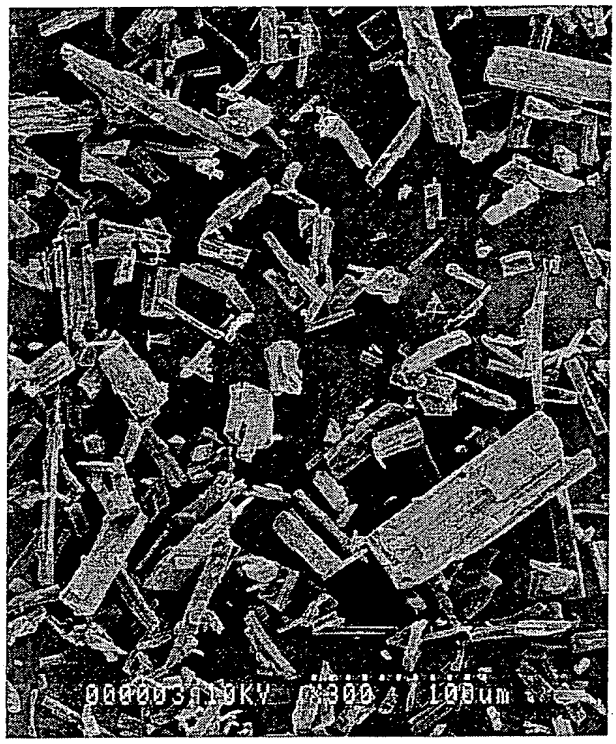
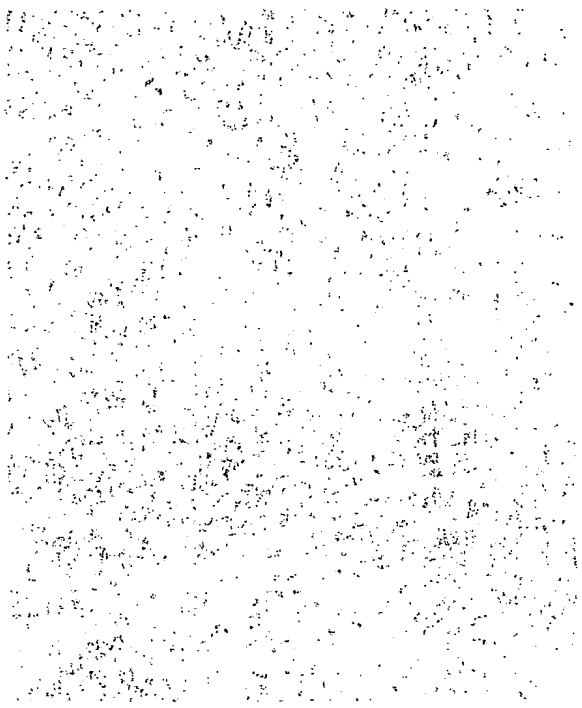


Figure 2:



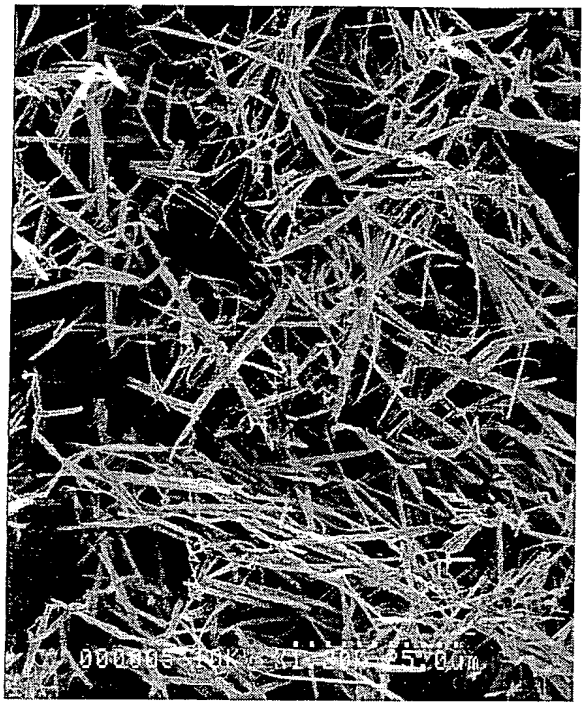
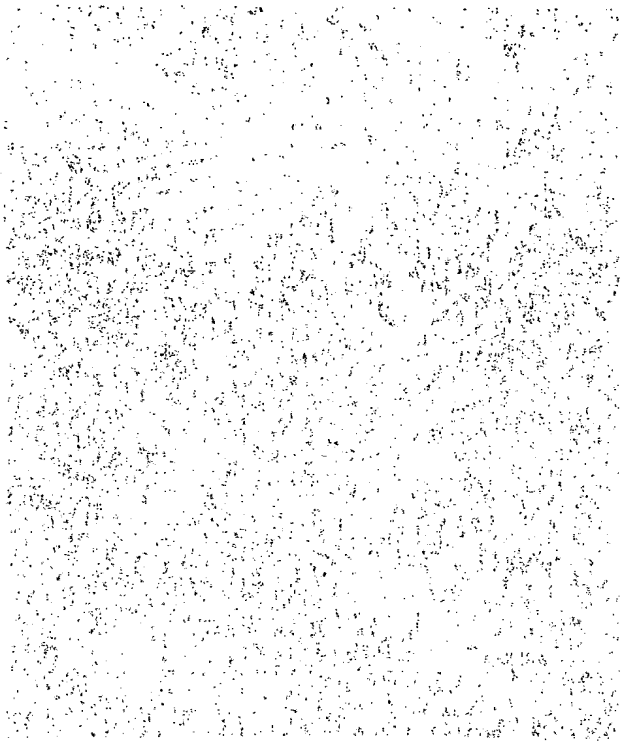


Figure 3.



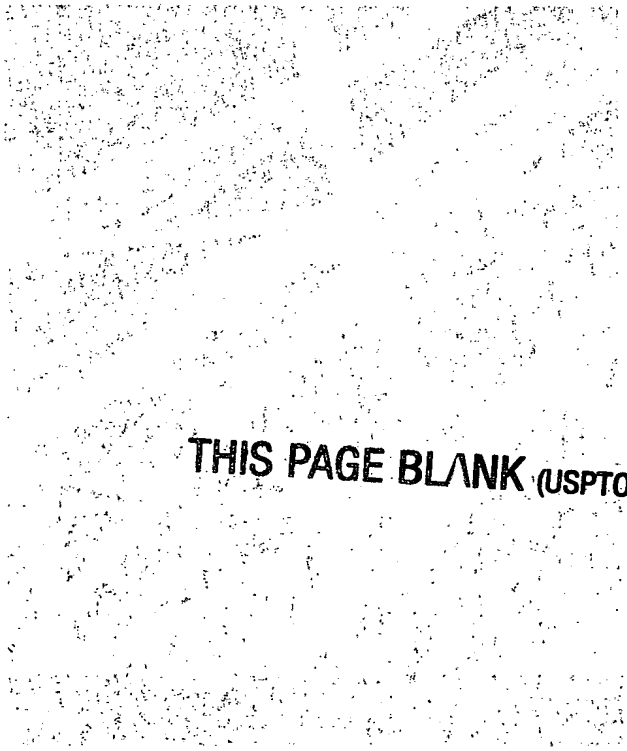


Figure 4

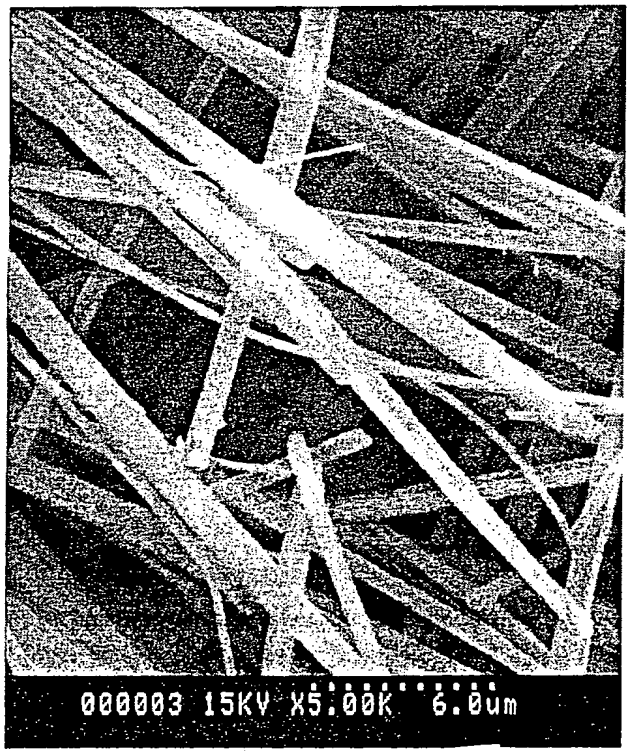
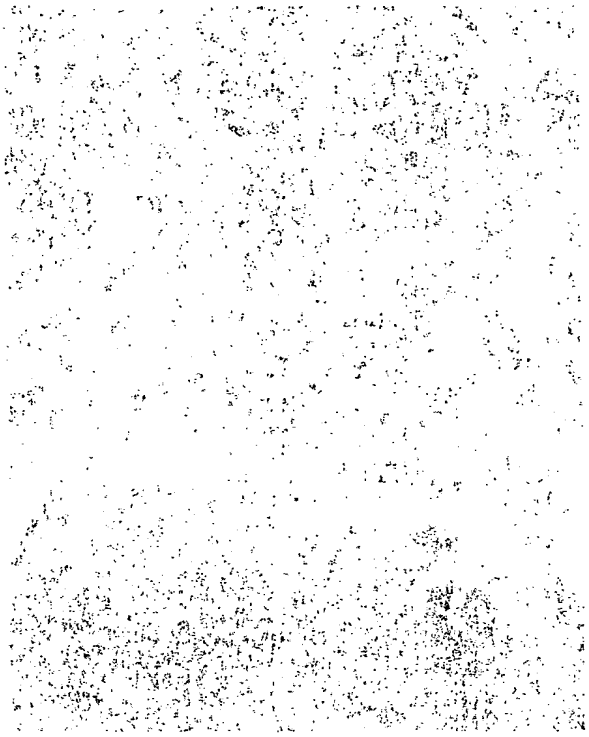


Figure 5



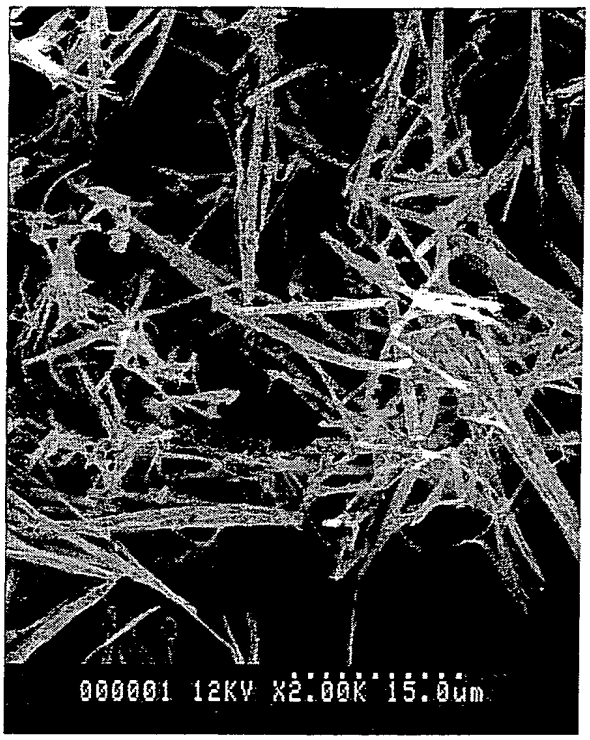
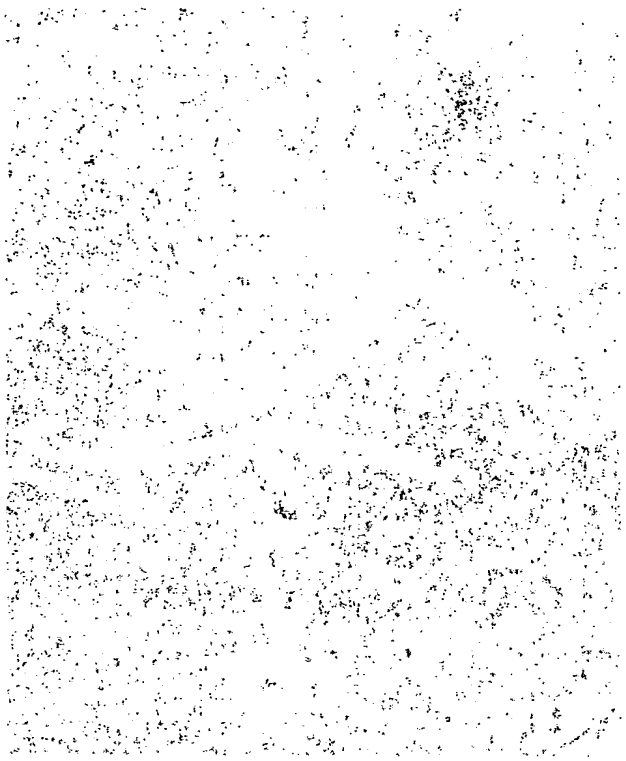
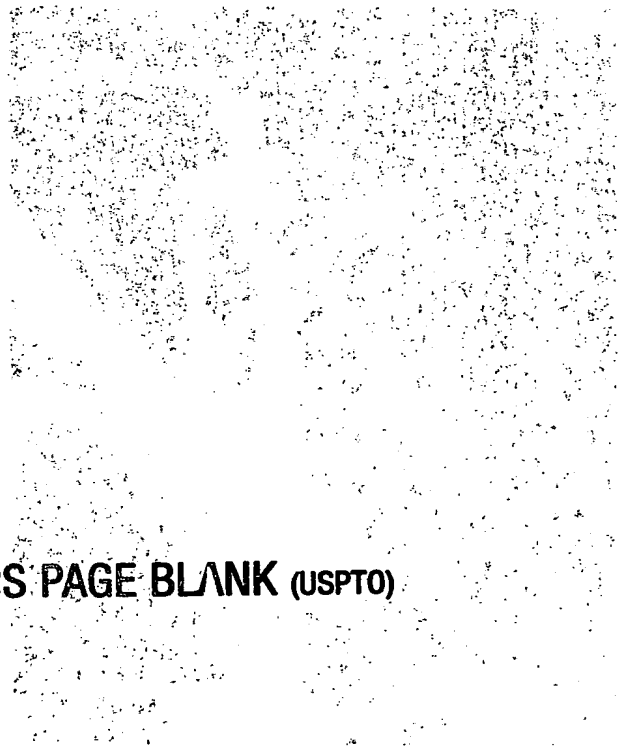


Figure **6**





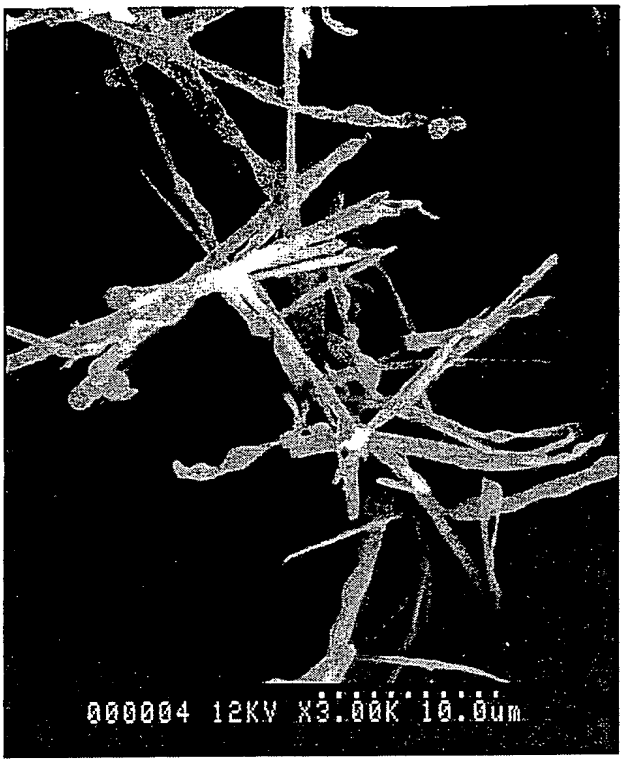


Figure 7

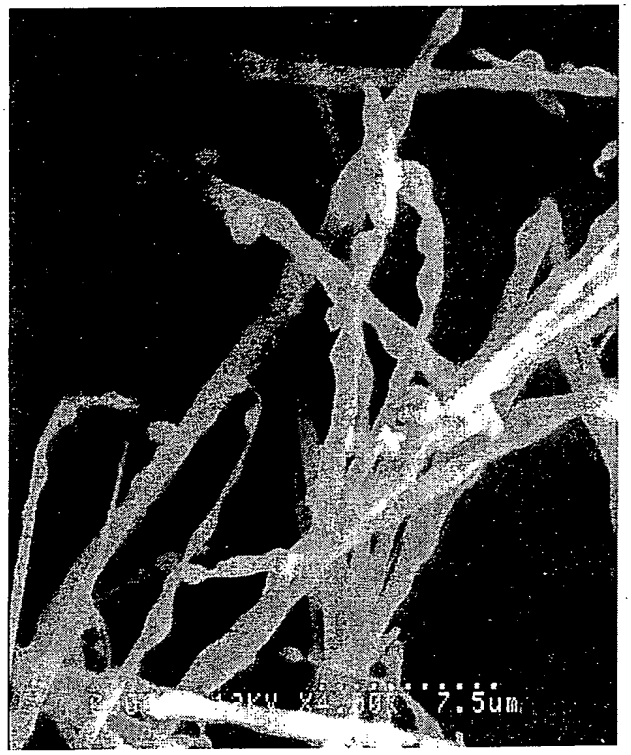
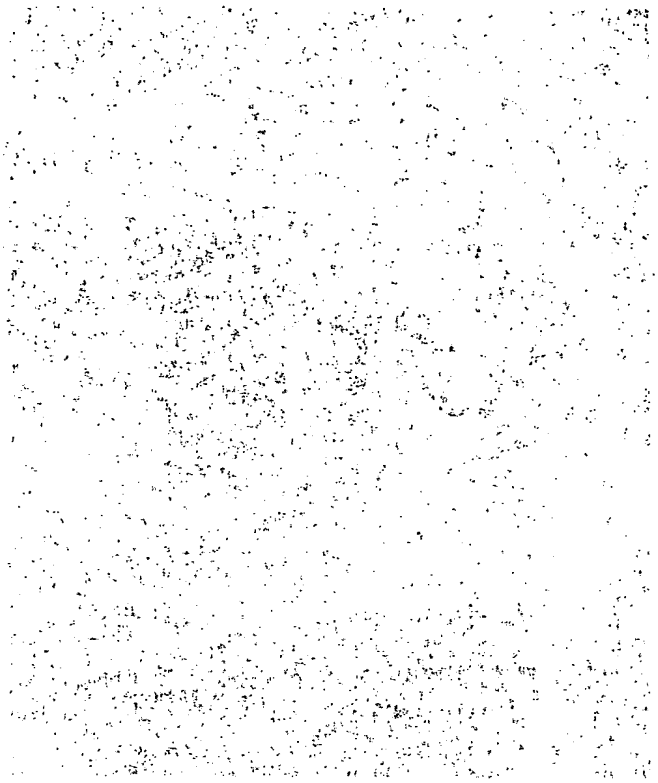
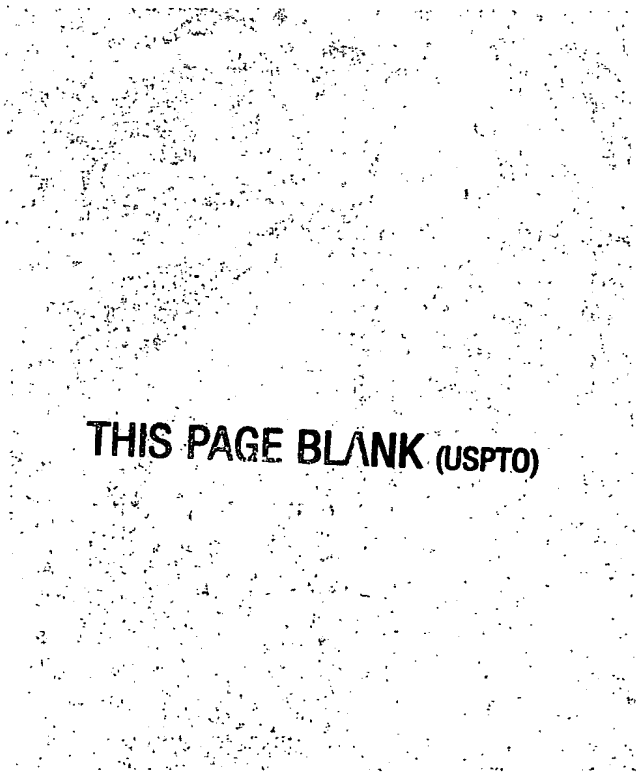


Figure 8

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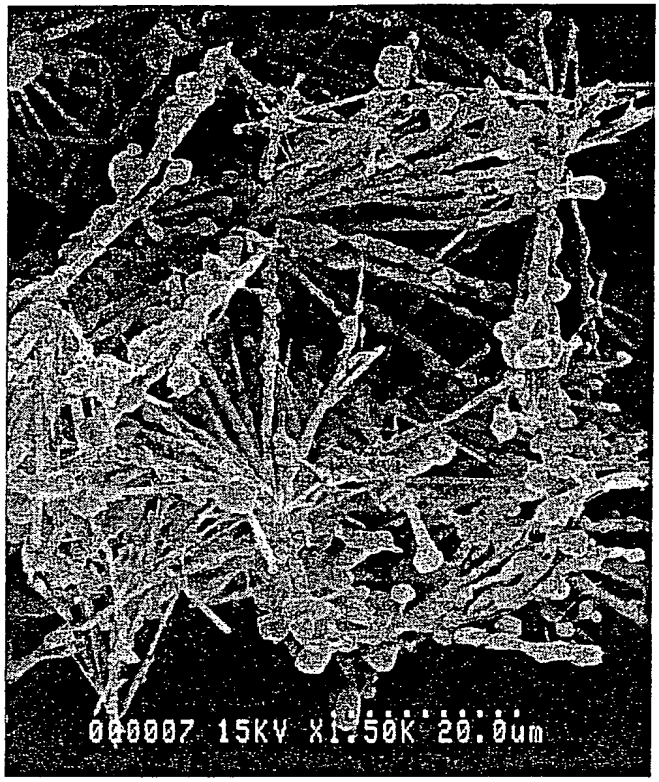


Figure 9

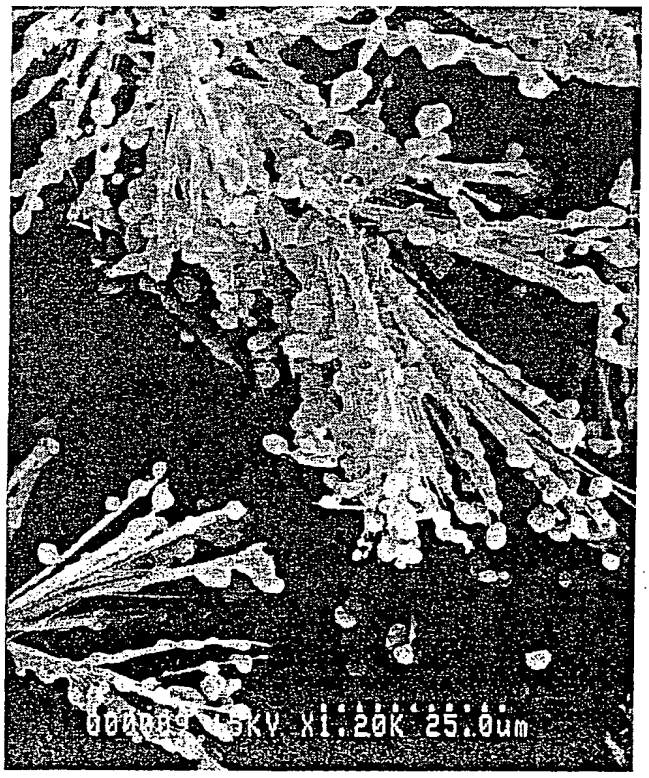


Figure 10

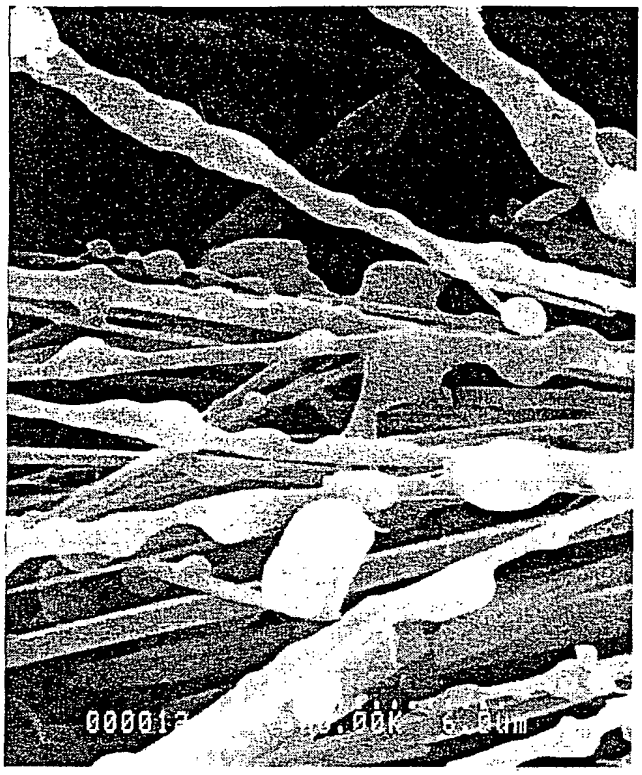
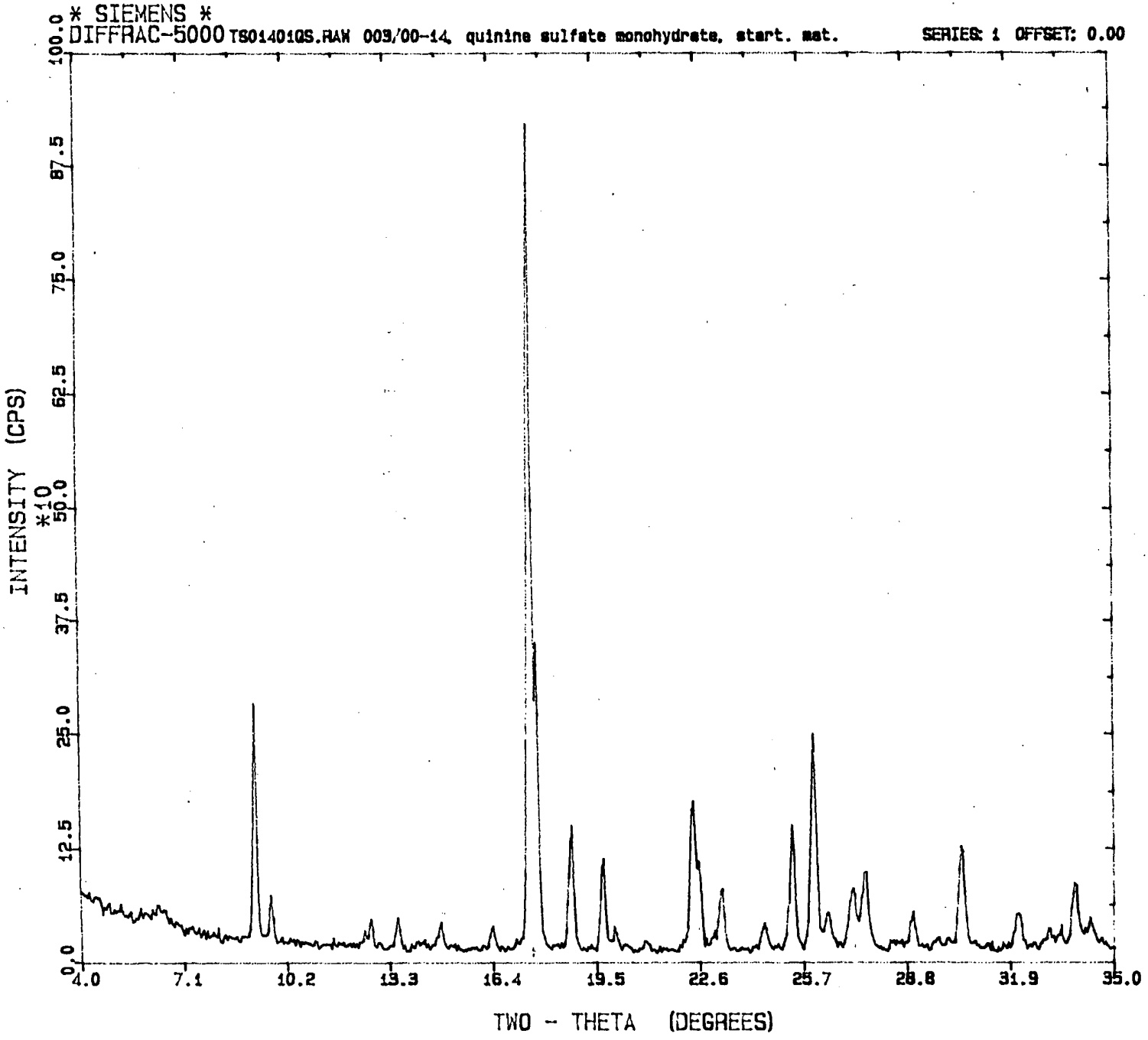


Figure 11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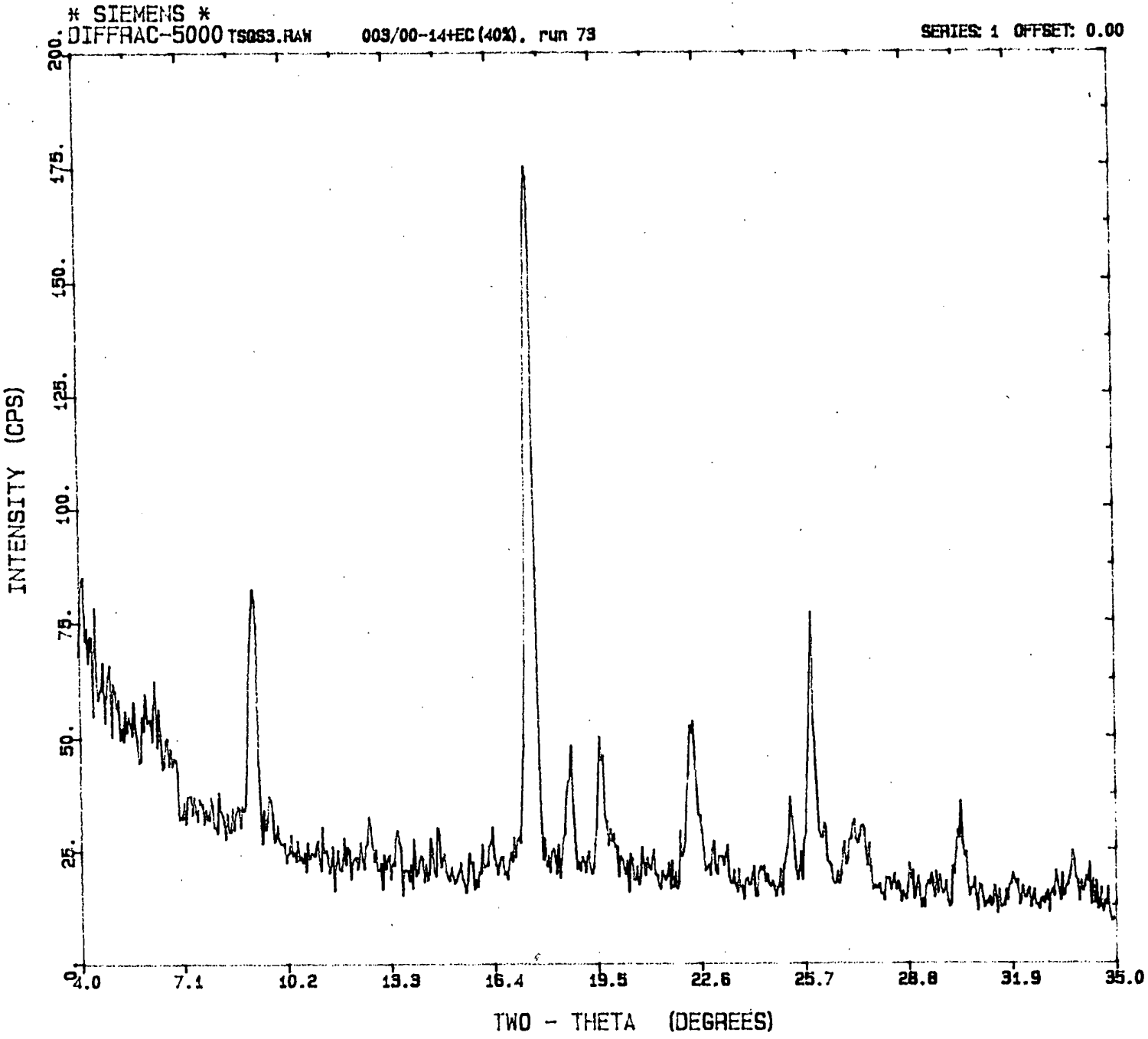
75.0
62.5
50.0
37.5
25.0
12.5
0.0
4.0
7.1
10.2
13.3
16.4
19.5
22.6
25.7
28.8
31.9
35.0
TWO - THETA (DEGREES)

FIGURE 12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003/00-14+EC(40%). run 73
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INTENSITY (CPS)
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175.
150.
125.
100.
75.
50.
25.
0.
4.0
7.1
10.2
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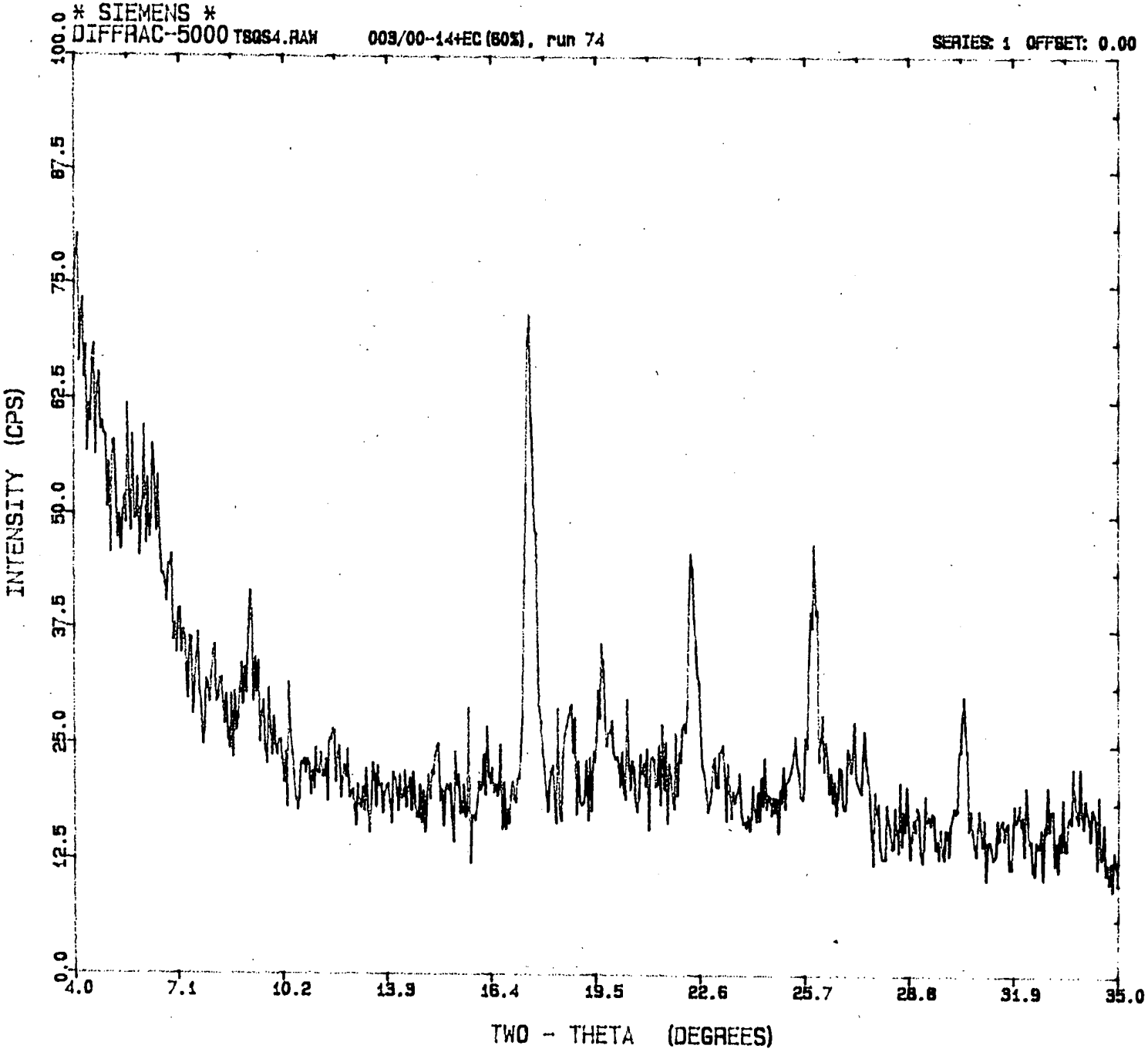
35.0
TWO - THETA (DEGREES)

FIGURE 13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25.0
12.5
0.0
4.0
7.1
10.2
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28.8
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35.0
TWO - THETA (DEGREES)

FIGURE 14

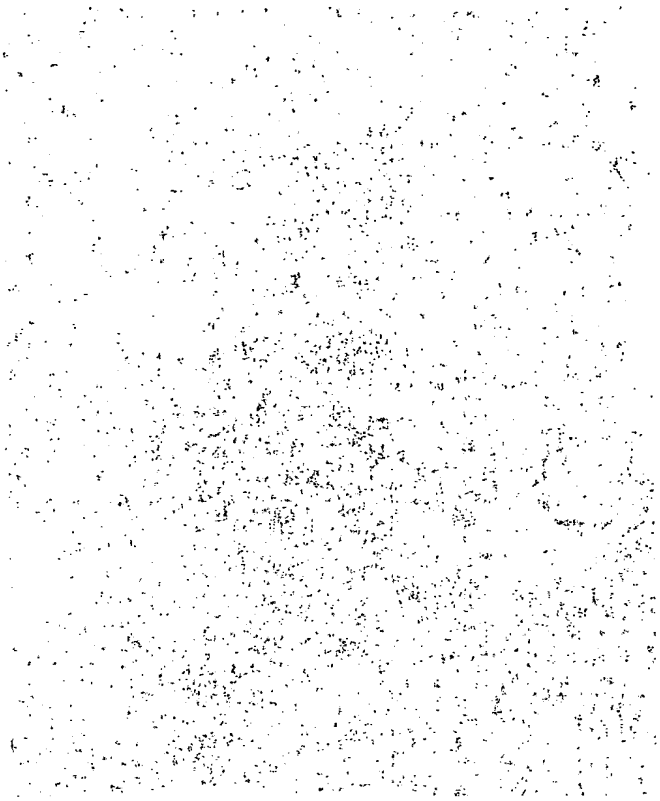
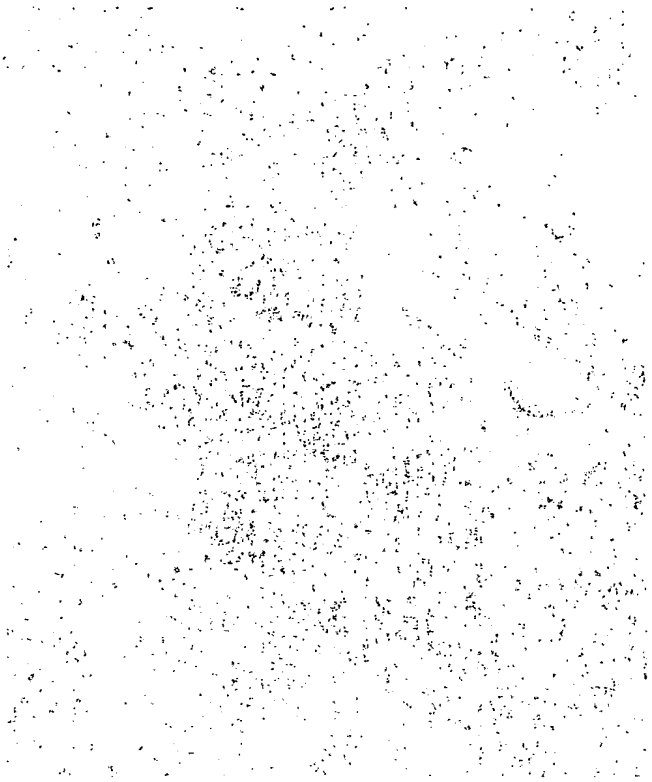


Figure 15

Figure 16



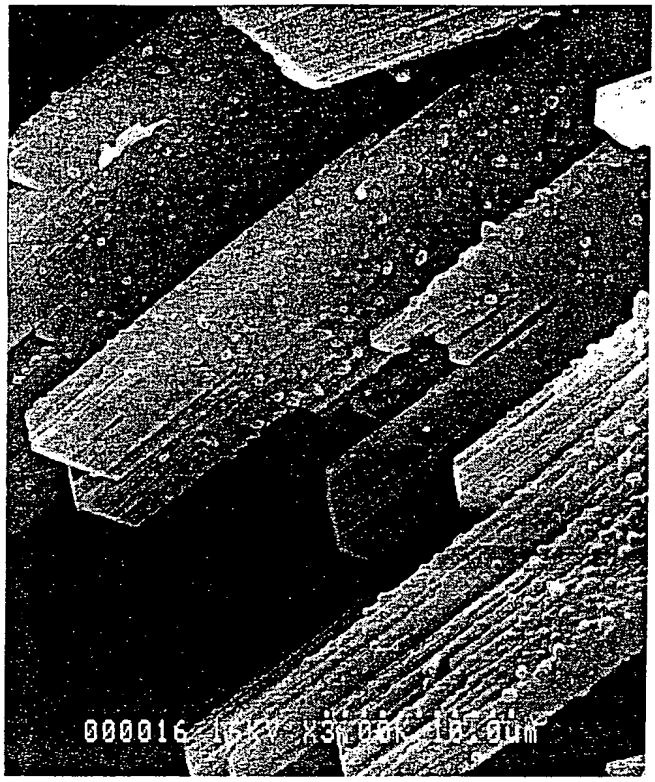


Figure 17

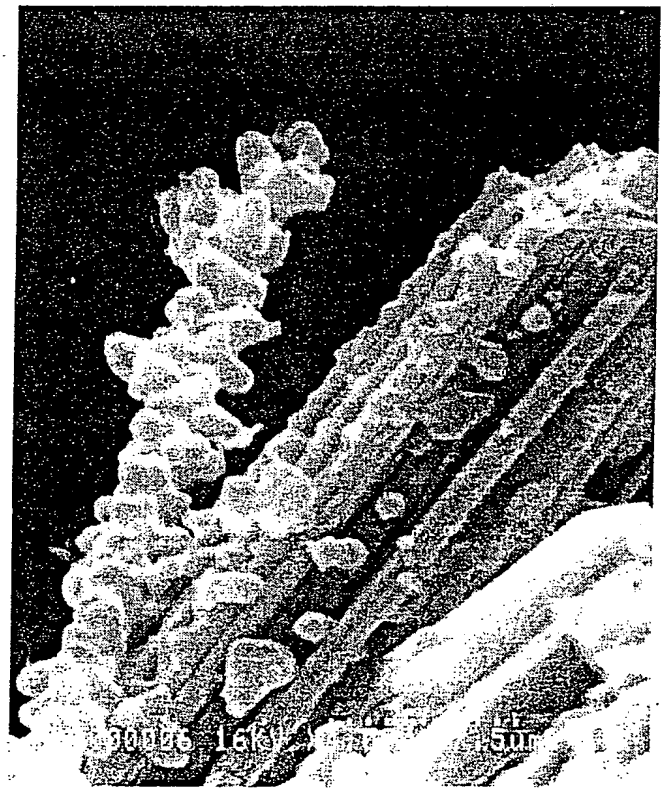
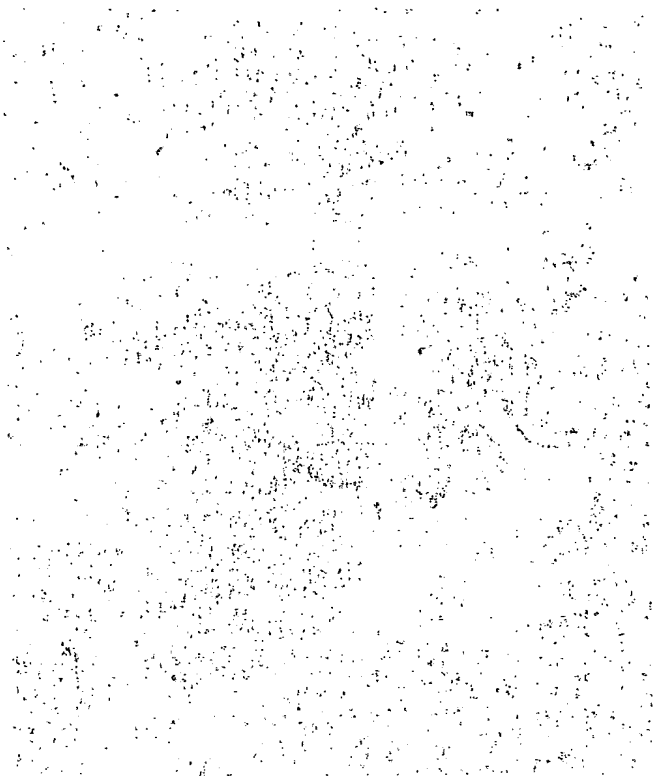


Figure 18



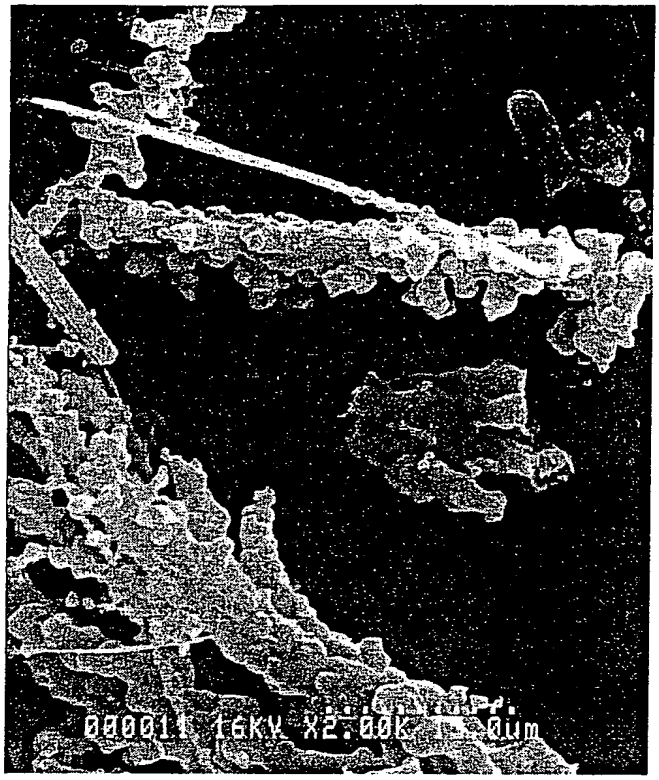


Figure 19

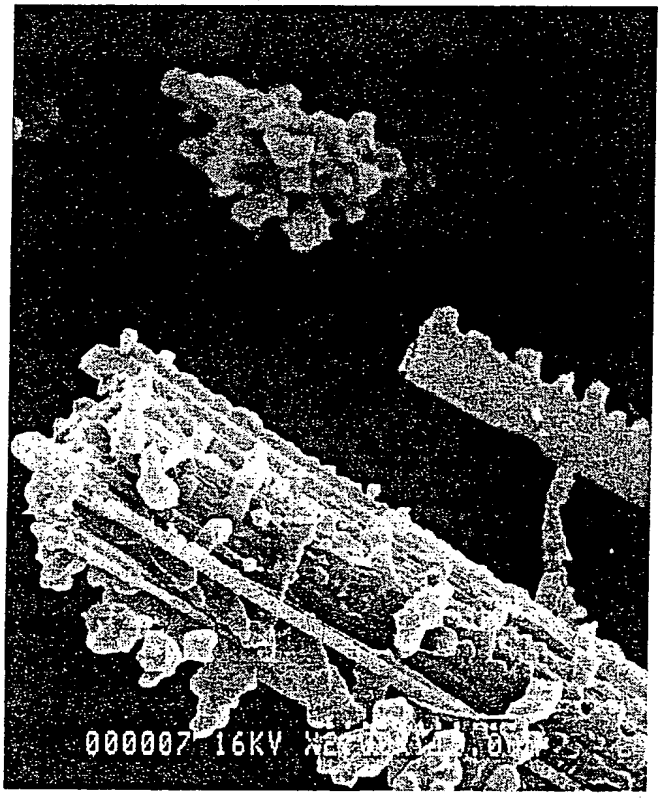


Figure 20

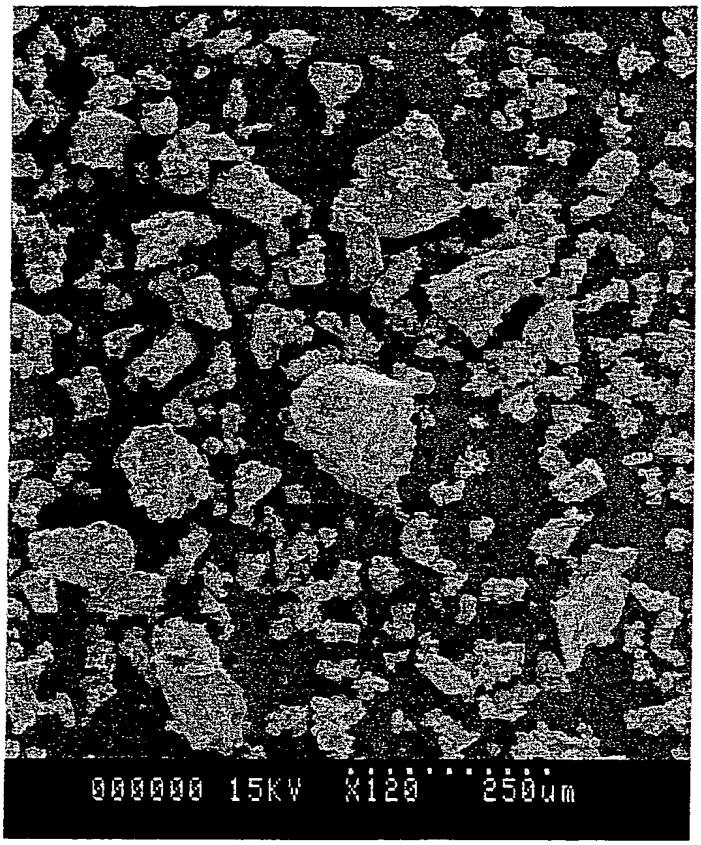


Figure 21

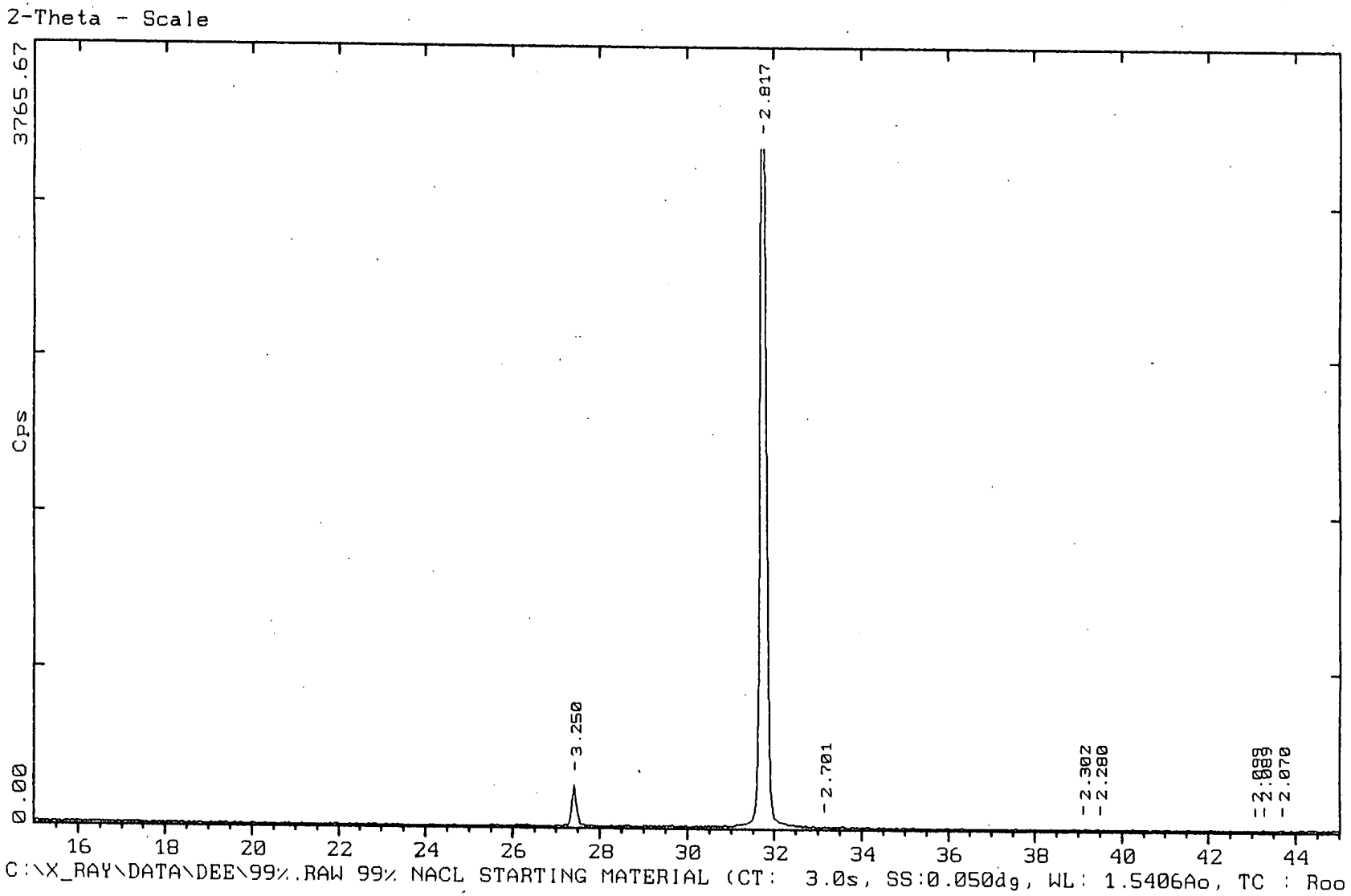

2-Theta - Scale
3765.67
Cps
0.00
- 2.817
- 3.250
- 2.701
- 2.302
- 2.280
- 2.089
- 2.070
16
18
20
22
24
26
28
30
32
34
36
38
40
42
44
C:\X_RAY\DATA\DEE\99%.RAW 99% NACL STARTING MATERIAL (CT: 3.0s, SS:0.050dg, WL: 1.5406Ao, TC : Roo

FIGURE 24

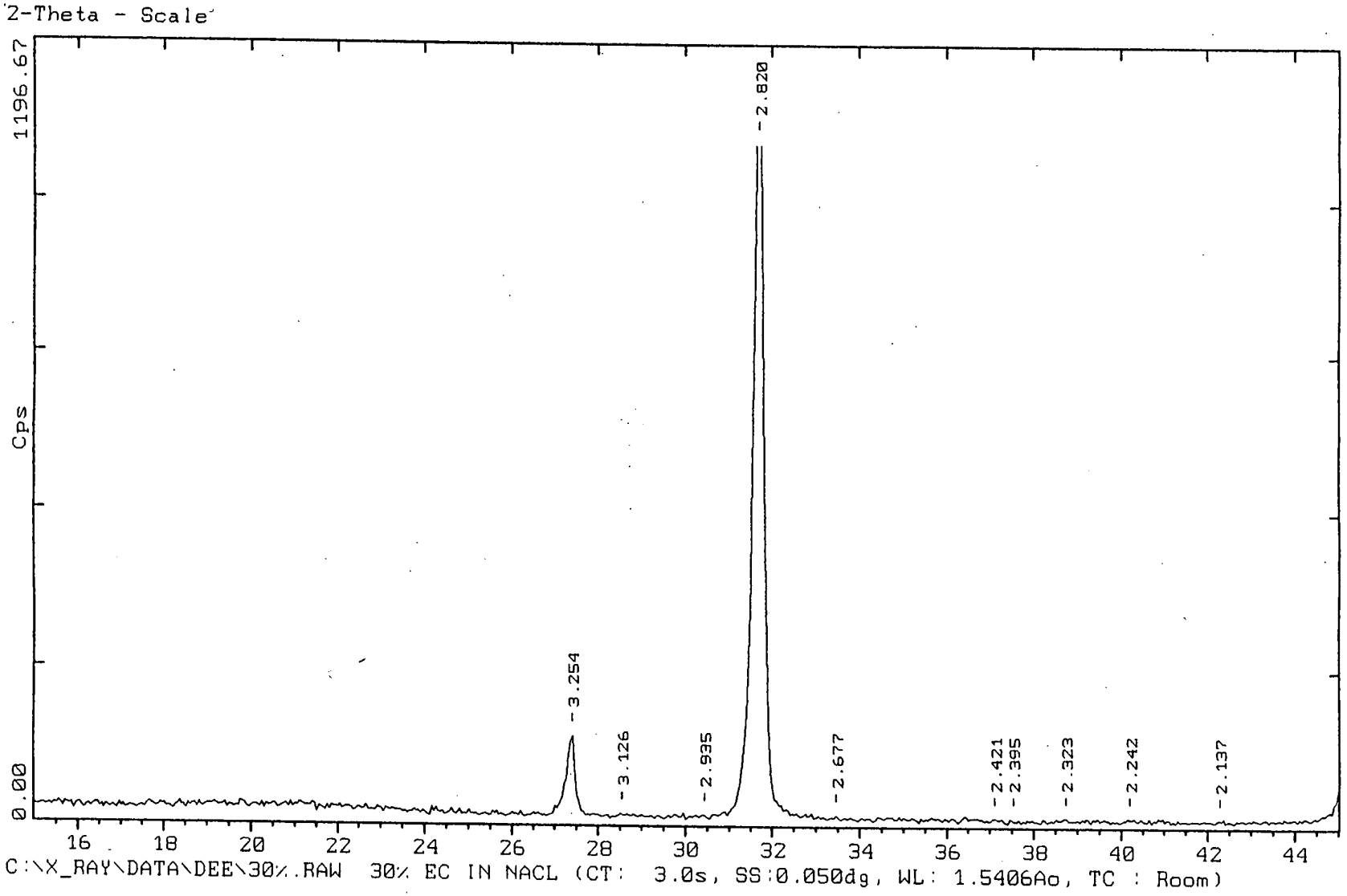

2-Theta - Scale
1196.67
Cps
0.00
16
18
20
22
24
26
28
30
32
34
36
38
40
42
44
3.254
3.126
2.935
2.820
2.677
2.421
2.395
2.323
2.242
2.137
C:\X_RAY\DATA\DEE\30%.RAW 30% EC IN NACL (CT: 3.0s, SS:0.050dg, WL: 1.5406Ao, TC : Room)

FIGURE 25